08/724,752 10/02/96

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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
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ZISKA, V.
EXAMINER

1804
ART UNIT | PAPER NUMBER

1809 08/05/97

DATE MAILED:

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 1/17/97

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire _____ month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 45 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 45 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

This application should be reviewed for errors.

Claims 1-44 have been cancelled; claim 45 has been newly added; claim 45 is active and examined in this Office Action.

Applicant's request for establishment of potential interference proceedings is denied. Contrary to applicant's arguments, applicants were not the first to invent the claimed subject matter since applicant's specification is not enabling for the invention patented to Lonberg et al., now USPN 5,545,806. The following is considered to represent a complete response to applicant's preliminary amendment, filed 1/17/97. No argument therein was found to be persuasive.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 45 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The instant specification fails to disclose a transgene capable of undergoing isotype switching. Applicants have argued on page 12 of the preliminary amendment that the '008 application discloses a transgene in which the number of nucleotides between mu and gamma are less than in the human germline and point to specific sections of the '008 specification. However, applicant's specification is merely prophetic for all aspects of the transgene. Applicant's specification does not specifically and clearly point to a transgene having the characteristics of the Lonberg transgene. Applicant's best phraseology, variously presented as "a fragment

of the human immunoglobulin subunit locus", "at least one xenogeneic constant region capable of being spliced to a functional J region", "at least a functional portion of human immunoglobulin loci for a heavy chain", "at least a functional portion of human immunoglobulin loci for a least a portion of the heavy chain" does not describe "a transgene in which the number of nucleotides between mu and gamma are less than in the human germline".

On page 12 of the amendment, Applicants have argued that the '008 application discloses a transgene in which the number of nucleotides between mu and gamma are less than in the human germline; that the application discloses transgene in which the functional portion of the heavy chain comprises "at least one constant region"; that the application further states that the disclosed strategies for producing the xenogeneic antibodies are based on knowledge of the organization and location of exons encoding domains and splice sites in the immunoglobulin loci and that the application states that using the methods of the invention any gamma subtype may be produced. However, the foregoing merely restates what was known in any immunology textbook at the time the '008 application was filed and does not specifically point out and direct one of skill to envision "a transgene in which the number of nucleotides between mu and gamma are less than in the human germline".

Applicants' arguments on page 13 directed to "A transgene encoding a gamma-2 antibody, thus may comprise, e.g., two constant region segments, mu and gamma-2 which are not contiguous in the human germline; such a transgene has fewer nucleotides between the transgene encoded mu and the transgene encoded gamma segments than in the human germline" do not have support in the '008 specification since the '008 specification did not specifically disclose "a transgene in which the number of

nucleotides between mu and gamma are less than in the human germline". Applicants have picked and chosen among phrases and sentences from the '008 specification in order to argue support for the their invention. However, the '008 specification fails to clearly contemplate or disclose the isotype switching transgene.

The requirements of a specification to support and enable an invention are clear. The specification must enable one of skill to make and use the invention as claimed. The '008 specification fails to provide an adequate written description of the transgene and further fails to enable one of skill to make the transgene capable of undergoing isotype switching. The Cox declaration, of record in the Lonberg application and now available to public, states that the method employing YACs disclosed and contemplated by the '008 specification was not, and could not, be cloned at the time the claimed invention was made, and secondly, in view of references with significantly later postfiling publication dates specifically stating that isotype switching to downstream isotypes had not yet been achieved using the described human Ig loci contained in YACs.

The Cox declaration states that there were no reports of the cloning in YAC vectors of the region spanning the human delta and gamma3 genes. This region is not readily or predictably cloned and the problem, as explained by the declarant, is possibly due to instability of that region of the human genome in certain cloning vectors, such as YACs. Thus, the art had not reported the cloning of an intact human IgH locus containing the V, D, J, mu, delta and gamma sequences, let alone an intact human IgH locus cloned in a YAC.

The published art was not aware of how to make a transgenic animal containing a transgene capable of undergoing isotype switching to produce human isotypes downstream of IgM as evidenced by Taki et al (1993), disclosing that the authors did

not know how to make a transgene that could undergo cis-isotype switching where endogenous sequences were not involved. Morrison, writing a review of the field in Nature (1994), discussed the teachings of Green et al., which referenced two Kucherlapati published PCT applications, (page 812, column 2, bottom):

"In Green and colleague's mice, only the mu heavy chain contributes significantly to the circulating antibody population, and these mice are unable to undergo the isotype switching characteristic of the mature antibody response. But in the mice of Lonberg et al., the heavy-chain locus contains both a mu and gamma1 heavy chain with switch sites, and these authors show that class switching occurs. So they have reconstituted the essential part of a human-antibody-producing response in a mouse and the system could be used both to study control of antibody production as well as to produce specific human antibodies".

In view of the foregoing, the instant specification is not enabling for the human IgH locus containing the V, D, J, mu, delta and gamma sequences cloned into a YAC capable of undergoing isotype switching, nor for a transgenic animal containing the IgH locus-YAC.

The specification of the instant application regarding the actual production of transgenic mice containing human immunoglobulin genes produced by fusion of spheroplasts containing YACs with ES cells is speculative and does not present any working examples showing actual cloning of human immunoglobulins (monoclonals) and that if such mice were actually obtained, that human antibodies would be expressed from the human IgH locus. In view of the lack of actual working examples and evidence presented showing that the DNA containing the human immunoglobulin locus could not be obtained by applicant's method at the time the claimed invention was made, the specification is not enabling for the method, or animals produced by the method, as claimed. The above references and declarations have been cited

to applicants in other copending applications, specifically 08/112,848, and are available therein.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claim 45 is rejected under 35 U.S.C. 102(e) as being anticipated by Lonberg (USPN 5,545,806). Lonberg discloses the invention exactly as claimed. Therefore, the reference anticipates the claims.

No claim is allowed.

Papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO FAX center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG (30 November 15, 1989). The CM1 Fax Center number is (703) 305-3014 or (703) 308-0294.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Suzanne Ziska, Ph.D., whose telephone number is (703)308-1217. In the event the examiner is not available, the examiner's supervisor, Ms. Jacqueline Stone, may be contacted at phone number (703) 308-3153.

SUZANNE E. ZISKA
PRIMARY EXAMINER
GROUP 1800